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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,994	03/03/2004	Alberto Orfao De Matos Correia E Valle	DE MATOS CORREIA E VALLE	4880
25889	7590	05/07/2007	EXAMINER	
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1077 NORTHERN BOULEVARD			ART UNIT	PAPER NUMBER
ROSLYN, NY 11576			1641	
			MAIL DATE	DELIVERY MODE
			05/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/791,994	DE MATOS CORREIA E VALLE ET AL.
	Examiner	Art Unit
	Gailene R. Gabel	1641

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 12 February 2007.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-35 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-35 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____. |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>3/3/04</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| | 6) <input type="checkbox"/> Other: _____. |

DETAILED ACTION

Election/Restrictions

1. Applicant's election of bone marrow species for neoplastic samples and hematopoietic cells for tumor types, filed on February 12, 2007, is acknowledged. However, upon further consideration the species election requirement, is being withdrawn. Accordingly, the list of neoplastic samples and tumor cells recited in the claims have been rejoined for prosecution on the merits. Accordingly, claims 1-35 are pending and are under examination.

Specification

2. The use of the trademark ALEXA FLUOR, ALEXA 647, and other trademarks, has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Abstract

3. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 step b) lacks antecedent basis in reciting, "the tumor sample."

Claim 1, step c) is ambiguous in reciting, "storing two independent list mode files, one containing information on the specific light scatter and fluorescence characteristics of each cell analyzed from the ... sample" because it is unclear as to whether the recited "information" refers back to sequential measurement information as obtained from step b); or are they standard information from any combination of normal/reactive sample and neoplastic sample. For clear antecedent basis, perhaps Applicant intends, "one containing measurement information ... from the normal/reactive samples in step

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b) and the other containing measurement information ... from the neoplastic sample in step b)."

Claim 1, step d) is also ambiguous in reciting, "creating new data files, by merging ... data file containing information about the cells present in the ... sample" because it is unclear as to whether the recited "information" again refers back to the sequential measurement information as obtained from step b); or are they standard information from any combination of normal/reactive sample and neoplastic sample. For clear antecedent basis, perhaps Applicant intends, "creating new data files from step c), by merging ... data file containing measurement information about the cells present in the ... samples in step b)."

Claim 1, step e) is ambiguous in appearing to have improper antecedent basis problem in reciting, "defining in a multidimensional space generated by the flow cytometric measurements... those areas corresponding to normal cells ...to empty spaces in normal/reactive samples and that may be occupied by tumor cells in neoplastic samples;" because it appears that the multidimensional space should be defined by pre-established standards, rather than those obtained from the measured samples. If so, then perhaps step e) should recite, "defining in a multidimensional space generated by flow cytometric measurements from pre-established standards... those areas corresponding to normal cells ...to empty spaces in normal/reactive samples and that may be occupied by tumor cells in neoplastic samples;"

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Claim 1, step f) is vague and indefinite in reciting, "sequentially identifying in the data files as described in step e)" because there are no data files described in step e). Perhaps, Applicant intends, "sequentially identifying in the data files obtained in step d)."

Claim 1, step f) has improper antecedent basis problem in reciting, "a multidimensional space". It should recite, "the multidimensional space" as it refers to that recited in step e).

Claim 1, step f) is confusing because it does not clearly define which flow cytometric measurements of light scatter and fluorescence emissions are being referred to, as it appears that there should be pre-established reference standard flow cytometric measurements and sample, i.e. normal/reactive and neoplastic, flow cytometric measurements encompassed and recited so as to enable sequential identification of different cellular events. Please clarify.

Claim 1, step g) is vague and indefinite, rendering claim 1 incomplete in failing to clearly define how phenotypic aberrations are identified as required by the preamble. Specifically, step g) only recites "establishing the most relevant phenotypic aberrations displayed by the neoplastic cells as compared to their normal counterparts" without specifically defining how the "most relevant phenotypic aberration is established" so as to allow "their unequivocal, sensitive and specific identification". Are the phenotypic aberrations manifested in a separate distinct multidimensional space from the neoplastic cells and their normal counterparts? Please clarify. Additionally the phrases,

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“most relevant”, “unequivocal” and “sensitive” are relative and subjective terms that lack comparative bases for defining their metes and bounds.

Claim 13 is vague and indefinite because it is unclear what Applicant intends to encompass in reciting, “stained directly after being obtained”, considering the nature of the label being used. Does Applicant intend directly at blood collection?

Claim 16 is ambiguous in reciting, “the panel of multiple combinations of monoclonal antibodies ...are shorter than” because the term “shorter” is a subjective and relative term that lacks a comparative basis for defining its metes and bounds, i.e. how is a panel shorter than another panel: in terms of number of types of antibodies or concentration of antibodies. It is further unclear how a “former panel is fully contained in the latter.” If Applicant intends to imply consonance in labeled monoclonal antibody cocktail between the combination that is contacted to the neoplastic samples and the combination that is contacted to the normal/reactive samples, but with the inclusion of more labeled monoclonal antibodies into the cocktail that is subjected for contact with the normal/reactive samples, then it should be recited as such, so as to render clear the claimed invention.

Claim 18 is indefinite because it is unclear as to whether the number of monoclonal antibodies contained in a combination is composed of “four or more monoclonal antibodies”, rather than “four or more monoclonal antibody reagents”. If Applicant indeed intends, “four or more monoclonal antibody reagents”, then it is unclear what structural and functional cooperative exists between the recitation of

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"combination of monoclonal antibodies" and the recitation of "monoclonal antibody reagents" because "four or more monoclonal antibody reagents" is not limited to "four or more monoclonal antibodies." Same analogous comments and problems apply to claim 19.

Claim 22 recites improper Markush language in reciting, "selected from." Change to "selected from the group consisting of" for proper Markush language.

Claim 22 is indefinite in reciting, "compatible" because the term "compatible" is a subjective term that lacks a comparative basis for defining its metes and bounds. Additionally, the phrase "or any additional compatible fluorochrome" renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "or any additional compatible fluorochrome"), thereby rendering the scope of the claim unascertainable. See MPEP § 2173.05(d).

Claim 22 is confusing because it is unclear what specific "compatible" fluorochromes Applicant intends to encompass. Applicant appears to list a set of individual fluorochromes and then another list of interchangeable fluorochromes; hence, it is unclear which list of fluorochromes are "compatible" with which. Note also the improper usage of trademarks in the claim.

Claim 23 lacks clear antecedent basis in reciting, "... panel used to stain different replicate aliquots of the same sample" because claim 1 from which it depends, does not appear to recite "replicating aliquots of the same sample". It is therefore, unclear how

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such limitation herein, specifically the “replicate aliquots of the same sample” is part of the recited method in claim 1. Same analogous comments and problems apply to claim 24.

Claim 26 is vague and indefinite because it is unclear how the limitations herein, specifically the “pre-established standards” are part of the recited method in claim 1. Accordingly, claim 26 lacks antecedent basis of relevant reference to “pre-established standards”, in claim 1. Same analogous comments and problems apply to claims 27-33.

Claim 31 is indefinite because it is unclear how the surface of microparticles are covered with anti-immunoglobulin antibodies. Does Applicant perhaps intend that the microparticles have anti-immunoglobulin antibodies coated or immobilized thereto. See also claim 32.

In claim 34, the recitation of “once diluted” lacks clear antecedent basis because there does not appear to be a step wherein the neoplastic cells are diluted with normal or reactive samples.

Claim 35 is confusing in reciting, “wherein abnormal patterns of antigen expression related to cell activation and a cell function are detected” because it is unclear how detection of cell activation and cell function is performed based on limitations recited in claim 1.

Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for a multiparametric flow cytometry method for identification of certain aberrant phenotypes expressed by neoplastic cells using multiple cocktail combinations of differentially fluorescent-labeled monoclonal antibodies specific for (1) CD22 / CD23 / CD19 / CD45 / CD5; (2) CD43 / CD79b / CD19 / CD45 / CD5; (3) anti-Lambda/ anti-Kappa / CD19 /CD45 / CD5; (4) anti-IgM / CD27 / CD19 / CD45 / CD5; (5) CD11c / CD10 / CD19 / CD45 / CD5; (6) CD103 / CD25 / CD19 / CD45 / CD5; and (7) CD20 / Zap70 / CD19 / CD45 / CD5, does not reasonably provide enablement for flow cytometry method for identification of aberrant phenotypes expressed by neoplastic cells using any overlapping multiple combinations of differentially fluorescent-labeled monoclonal antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As set forth in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working

examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a method of identifying aberrant phenotypes expressed by neoplastic cells wherein a series of duplicate aliquots of normal/reactive cells and neoplastic cells from blood or bone marrow sample, are separately stained with overlapping multiple combinations of differentially fluorescent-labeled monoclonal antibodies, each combination having in common at least three fluorochrome-conjugated monoclonal antibodies. These combinations of monoclonal antibodies are (1) CD22 / CD23 / CD19 / CD45 / CD5 specific MAbs; (2) CD43 / CD79b / CD19 / CD45 / CD5 specific MAbs; (3) anti-Lambda/ anti-Kappa / CD19 /CD45 / CD5 specific MAbs; (4) anti-IgM / CD27 / CD19 / CD45 / CD5 specific MAbs; (5) CD11c / CD10 / CD19 / CD45 / CD5; (6) CD103 / CD25 / CD19 / CD45 / CD5 specific MAbs; and (7) CD20 / Zap70 / CD19 / CD45 / CD5 specific MAbs. Each of the stained cells are then sequentially measured for light scattering properties and fluorescence intensity or emissions using multiparametric flow cytometry; and the measurement information for the normal/reactive cells and the neoplastic cells are stored in two independent list mode data files, from which known proportions of cellular events are merged into new data file. Events corresponding to neoplastic cells different from those corresponding to normal/reactive cells are identified in defined multidimensional spaces, whereupon phenotypic aberrations are displayed and identified.

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The state of the prior art- the prior art of record discloses a method of identifying aberrant phenotypes expressed by neoplastic cells, as claimed, wherein a series of duplicate aliquots of normal/reactive cells and neoplastic cells from bone marrow sample, are separately stained with multiple combinations of differentially fluorescent-labeled monoclonal antibodies, each combination having in common one fluorochrome-conjugated monoclonal antibody between each of the combinations 1) CD10-FITC / CD19-PE / HLA-DR PerCP; 2) CD34-FITC, CD22-PE, CD20-PerCP; 3) CD34-FITC / CD38-PE / HLA-DR-PerCP; 4) CD1-FITC / CD5-PE / CD20-PerCP; 5) CD7-FITC / CD33-PE / CD3-PerCP; 6) CD13-FITC / CD14-PE / HLA-DR-PerCP; 7) CD2-FITC / CD11c-PE / CD34-PerCP; 8) α -glycophorin A FITC / CD71-PE / CD45-PerCP; and 9) CD15-FITC / CD11b-PE / CD34-PerCP.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the claimed method will work to identify aberrant phenotypes of neoplastic cells using any combination of monoclonal antibodies having at least three monoclonal antibodies in common, therebetween.

The amount of direction or guidance present- appropriate guidance is provided by the specification for the claimed method to work in identifying aberrant phenotypes of neoplastic cells using overlapping multiple combinations of differentially fluorescent-labeled monoclonal antibodies, each combination having in common at least three fluorochrome-conjugated monoclonal antibodies. These combinations of monoclonal antibodies are (1) CD22 / CD23 / CD19 / CD45 / CD5 specific MAbs; (2) CD43 / CD79b / CD19 / CD45 / CD5 specific MAbs; (3) anti-Lambda/ anti-Kappa / CD19 /CD45 / CD5

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specific MAbs; (4) anti-IgM / CD27 / CD19 / CD45 / CD5 specific MAbs; (5) CD11c / CD10 / CD19 / CD45 / CD5; (6) CD103 / CD25 / CD19 / CD45 / CD5 specific MAbs; and (7) CD20 / Zap70 / CD19 / CD45 / CD5 specific MAbs; and then multiparametrically measuring each of the labeled cells for light scatter and fluorescence intensity. However, the specification fails to provide guidance to enable the claimed method to function using any combination of monoclonal antibodies having at least three monoclonal antibodies in common.

The presence or absence of working examples- working examples are provided in the specification that show using overlapping multiple combinations of differentially fluorescent-labeled monoclonal antibodies, each combination having in common at least three fluorochrome-conjugated monoclonal antibodies. These combinations of monoclonal antibodies are (1) CD22 / CD23 / CD19 / CD45 / CD5 specific MAbs; (2) CD43 / CD79b / CD19 / CD45 / CD5 specific MAbs; (3) anti-Lambda/ anti-Kappa / CD19 /CD45 / CD5 specific MAbs; (4) anti-IgM / CD27 / CD19 / CD45 / CD5 specific MAbs; (5) CD11c / CD10 / CD19 / CD45 / CD5; (6) CD103 / CD25 / CD19 / CD45 / CD5 specific MAbs; and (7) CD20 / Zap70 / CD19 / CD45 / CD5 specific MAbs; and then multiparametrically measuring each of the labeled cells for light scatter and fluorescence intensity. There are no working examples that show analogous results using any other combination of monoclonal antibodies, which are encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed which

would encompass numerous other combinations of monoclonal antibodies specific for many other cell type populations.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a method of identifying aberrant phenotypes expressed by neoplastic cells wherein a series of duplicate aliquots of normal/reactive cells and neoplastic cells from blood or bone marrow sample, are separately stained with overlapping multiple combinations of differentially fluorescent-labeled monoclonal antibodies, each combination having in common at least three fluorochrome-conjugated monoclonal antibodies. Each of the stained cells are then sequentially measured for light scattering properties and fluorescence intensity or emissions using multiparametric flow cytometry; and the measurement information for the normal/reactive cells and the neoplastic cells are stored in two independent list mode data files, from which known proportions of cellular events are merged into new data file. Events corresponding to neoplastic cells different from those corresponding to normal/reactive cells are identified in defined multidimensional spaces, whereupon phenotypic aberrations are displayed and identified. As recited, aberrant phenotypes of neoplastic cells will be quantitatively identified and measured using any combination of fluorescent-labeled monoclonal antibodies, having three monoclonal antibodies in common, without specifically showing how it can be done without undue experimentation.

In this case, the specification states that the disclosed method provides sensitive, specific, and reproducible method of detecting aberrant phenotypes of protein expression in neoplastic cells in bone marrow and peripheral blood. The method comprises all the method steps recited in claim 1, steps a) – g) (see page 7, last full paragraph bridging to page 13, first full paragraph. A preferred embodiment of the claimed invention provides sequential acquisition of information on separate aliquots of sample/microparticle mixture stained with different combinations of monoclonal antibodies, the data of which are stored separately in different files but later on merged into a single data file (see pages 14-15). In pages 20-22 of the specification, six replicate tubes of peripheral blood sample is mixed with one of the following combinations of monoclonal antibodies, each one specific for: (1) CD22 / CD23 / CD19 / CD45 / CD5; (2) CD43 / CD79b / CD19 / CD45 / CD5; (3) anti-Lambda/ anti-Kappa / CD19 /CD45 / CD5; (4) anti-IgM / CD27 / CD19 / CD45 / CD5; (5) CD11c / CD10 / CD19 / CD45 / CD5; (6) CD103 / CD25 / CD19 / CD45 / CD5; and (7) CD20 / Zap70 / CD19 / CD45 / CD5; and each combination including three overlapping monoclonal antibodies, i.e. specific for CD19 / CD45 / CD5. After incubation, a PerfectCount microbead suspension is also added for each tube. Each aliquot is sequentially measured by multiparametric flow cytometer analysis wherein a single data file was collected for each tube which contained information on the forward angle light scatter (FSC), side angle light scatter (SSC), and fluorescence emissions of FITC, PE, PE-texas red, PE-CY5, and APC for all the fluorescent labeled cells and microbeads present in each tube. A neoplastic sample (B-CLL) is also tested in parallel as above.

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Clustering analysis for the merged NORMAL/B-CLL data files provided that in all NORMAL/B-CLL data files, a population of CD5+ / CD19+ / CD45 high / CD20 low / CD11c- / CD22- / CD23++ / CD43+ / CD79b low / IgM low / CD27+ / CD103- / CD25 low / kappa low / lambda- / ZAP70- / CD10- neoplastic B-cells expressing an aberrant phenotype can be identified, which is absent in the NORMAL data file (see page 24).

While the specification exemplifies multiparameter flow cytometric identification of neoplastic cells such as B-CLL using one of the following combinations of monoclonal antibodies, each one specific for: (1) CD22 / CD23 / CD19 / CD45 / CD5; (2) CD43 / CD79b / CD19 / CD45 / CD5; (3) anti-Lambda/ anti-Kappa / CD19 / CD45 / CD5; (4) anti-IgM / CD27 / CD19 / CD45 / CD5; (5) CD11c / CD10 / CD19 / CD45 / CD5; (6) CD103 / CD25 / CD19 / CD45 / CD5; and (7) CD20 / Zap70 / CD19 / CD45 / CD5; each combination including three overlapping monoclonal antibodies, i.e. specific for CD19 / CD45 / CD5, for admixture with PerfectCount microbead suspension, the specification does not show any working examples of the claimed method using any other overlapping multiple combinations of differentially fluorescent-labeled monoclonal antibodies specific for any and all cell surface antigens that are expressed in cell types present in all of normal or reactive and neoplastic bone marrow and peripheral blood cell samples. The fact that the claimed method appears to work in identifying aberrant phenotypes of proteins expressed by neoplastic cells using the listed overlapping multiple combinations of monoclonal antibodies specific for: (1) CD22 / CD23 / CD19 / CD45 / CD5; (2) CD43 / CD79b / CD19 / CD45 / CD5; (3) anti-Lambda/ anti-Kappa / CD19 / CD45 / CD5; (4) anti-IgM / CD27 / CD19 / CD45 / CD5; (5) CD11c / CD10 /

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CD19 / CD45 / CD5; (6) CD103 / CD25 / CD19 / CD45 / CD5; and (7) CD20 / Zap70 / CD19 / CD45 / CD5, is not sufficient to enable the breadth of the claimed method which recites use of any overlapping multiple combinations of monoclonal antibodies specific for any and all cell surface antigens that are present in bone marrow and peripheral blood samples, to perform the same function. The specification does not establish a direct correlation between results obtained from the disclosed multiple combinations consisting of (1) CD22 / CD23 / CD19 / CD45 / CD5; (2) CD43 / CD79b / CD19 / CD45 / CD5; (3) anti-Lambda/ anti-Kappa / CD19 /CD45 / CD5; (4) anti-IgM / CD27 / CD19 / CD45 / CD5; (5) CD11c / CD10 / CD19 / CD45 / CD5; (6) CD103 / CD25 / CD19 / CD45 / CD5; and (7) CD20 / Zap70 / CD19 / CD45 / CD5 and results obtained from any other combination of five monoclonal antibodies using the claimed invention, which would lead the skilled artisan to say that if the claimed method works using the cocktail of multiple monoclonal antibody combinations consisting of (1) CD22 / CD23 / CD19 / CD45 / CD5; (2) CD43 / CD79b / CD19 / CD45 / CD5; (3) anti-Lambda/ anti-Kappa / CD19 /CD45 / CD5; (4) anti-IgM / CD27 / CD19 / CD45 / CD5; (5) CD11c / CD10 / CD19 / CD45 / CD5; (6) CD103 / CD25 / CD19 / CD45 / CD5; and (7) CD20 / Zap70 / CD19 / CD45 / CD5, to identify aberrant phenotypes of proteins expressed by neoplastic cells from other populations, then it should work using any other multiple combination of monoclonal antibodies, to enable the breadth of the claimed method. While it is not necessary to show working examples for every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan that the breadth of the claimed method is enabled. This is not the case in the

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instant specification. Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 3, 6-13, 15-17, 19, 20, 23-25, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagler et al. (Detection of Minimal residual disease (MRD) after bone marrow transplantation (BMT) by multi-parameter flow cytometry (MPFC), Medical Oncology 16: 177-187 (1999)).

Nagler et al. teach a method for multiparameter flow cytometric detection and identification of aberrant phenotypes of protein expression by neoplastic cells in a bone marrow sample. Using the method, Minimal Residual Disease (MRD) is detected by identifying cells with aberrant antigen expression and/or leukemia-associated phenotype (see Abstract). The method utilizes abnormal positions of neoplastic (leukemic) cells in multidimensional space created by light scatter and immunofluorescence intensity parameters (see page 178, column 1). In practice, normal or reactive replicate cell samples and neoplastic replicate cell samples, i.e. from acute lymphoblastic leukemia (ALL) patients, are mixed with each one of the following fluorescent-labeled antibody combinations: 1) CD10-FITC / CD19-PE / HLA-DR PerCP; 2) CD34-FITC, CD22-PE, CD20-PerCP; 3) CD34-FITC / CD38-PE / HLA-DR-PerCP; 4) CD1-FITC / CD5-PE / CD20-PerCP; 5) CD7-FITC / CD33-PE / CD3-PerCP; 6) CD13-FITC / CD14-PE / HLA-DR-PerCP; 7) CD2-FITC / CD11c-PE / CD34-PerCP; 8) α -glycophorin A FITC / CD71-PE / CD45-PerCP; and 9) CD15-FITC / CD11b-PE / CD34-PerCP. As noted, each monoclonal antibody (MAb) for every cocktail or combination has a different label, so as to render them, differentially distinguishable (see page 178, column 2: Cell Preparation, and page 179, column 2, third full paragraph). Each of the combination of differentially fluorescent-labeled MAbs used to label the normal/reactive cells and the neoplastic cells have in common (i.e. same) overlapping MAbs included therein (MAbs specific to CD20, CD34, HLA-DR). For each pair of panels of MAb, an exact clone of each fluorescent-labeled MAb used in certain combinations, are identical in the two panels combinations. Each MAbs that are common to the combinations may vary depending on type, lineage,

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and maturation stage of the tumor cells (CD34-FITC, CD20-PerCP, and HLA-DR Per-CP) (see page 178, column 2: Cell Preparation). The MAbs can be selected depending on the type, lineage, and maturation stage of the tumor cells. As for patient populations used as source of cell samples, four healthy individuals with defined compatible age and gender group were used as normal, i.e. non-neoplastic control samples. Twenty-one leukemia patients represented the neoplastic samples (bone marrow aspirates) which contain different hematopoietic tumor cells such as lymphoblastic cells from ALL patients and myeloblastic cells from AML patients. The neoplastic samples are obtained at first diagnosis (pre-bone marrow transplant (BMT)), relapse (after complete remission), and at any time period after the diagnosis (post-BMT) (see page 17: subtitled *Patients* in column 1-2 and page 180, column 2 to page 182, column 2). The fluorescent labels conjugated with each one of the monoclonal antibodies have peak emission spectra each different from the other (FITC, PE, PerCP). Light scatter and fluorescence intensity of each of the labeled cells from each one of the normal/reactive samples and neoplastic sample, are measured sequentially using multiparameter flow cytometry (FACSAN) wherein 10,000 events are acquired and stored into independent listmode data files with a trigger on forward light scatter and subsequently, the remainder of each sample was read in which only cells with specific phenotypic and light scatter characteristics are acquired (see page 179, column 1, first full paragraph under *Flow Cytometry*). Analysis of data is performed using software program, i.e. PAINT-Agate or Cut-a-cluster, that merges information from the listmode data file for clustering into multidimensional data space based on flow cytometric measurements,

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and permits sequential identification in the data files of those events corresponding to neoplastic cells which differ from normal cells in the multiple cell populations that coexist in the multidimensional data space (see page 179, column 1, last full paragraph under Data Analysis to page 183, column 1) Aberrant phenotypes of neoplastic cells are identified and established using this multiparameter flow cytometric method between Pre-BMT, relapse, and post BMT patients (see page 183-184).

Nagler et al. differ from the claimed invention in failing to teach using combinations of monoclonal antibodies having in common at least three fluorochrome-conjugated monoclonal antibodies.

However, Nagler et al., indeed, teach single monoclonal antibody overlaps (MAbs specific to CD20, CD34, HLA-DR) in common between the monoclonal antibody combinations in page 178, column 2. It is maintained that the number and types of monoclonal antibodies used in common so as to overlap to select or deselect certain populations of cells in samples, encompass result effective variables which the prior art reference has shown may be altered in order to achieve optimum results. It has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454, 456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation." Id. at 458, 105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a

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known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272, 276, 205 USPQ 215, 218-219 (C.C.P.A. 1980). Since Applicant has not disclosed that the specific limitations recited in instant claims 1 and 18, reciting the commonality of three or more monoclonal antibodies for every combination used, are for any particular purpose or solve any stated problem, and Nagler et al. teach that types and numbers of monoclonal antibodies may vary according to the sample, cell type, and aberrant phenotypes being identified and analyzed, and various other combinations of fluorescent-labeled monoclonal antibodies appear to work equally as well for their purposes; absent unexpected results, it would have been obvious for one of ordinary skill to discover the optimum workable ranges of the methods disclosed by the prior art by normal optimization procedures known in cell-based multiparametric flow cytometry art.

7. Claims 2, 4, 5, 18, 21, 22, 26, 27, and 30-33 rejected under 35 U.S.C. 103(a) as being unpatentable over Nagler et al. (Detection of Minimal residual disease (MRD) after bone marrow transplantation (BMT) by multi-parameter flow cytometry (MPFC), Medical Oncology 16: 177-187 (1999)) in view of Ward et al. (US Patent 5,627,037).

Nagler et al. is discussed supra. Nagler et al. differ from the instant invention in failing to teach using peripheral blood, bone marrow, spinal fluid, and lymph node sample. Nagler et al. also does not teach using reference microparticles used as pre-established standards in the method.

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Ward et al. disclose a method for multiparameter detection, enumeration, and absolute counting of cell populations in a blood sample. The sample is a body fluid which is any one of peripheral blood, bone marrow, cerebrospinal fluid, and lymph node (see Abstract and column 5, lines 34-41). The method is specifically for counting different subsets of cells in whole blood including monocytes, lymphocytes, and granulocytes by using a cocktail of monoclonal antibodies to CD45, CD14 and CD15; and additionally can be extended to identifying and counting T lymphocytes or B lymphocytes by further using monoclonal antibodies to CD3 and CD19 or CD20. Hence, there may be four or more monoclonal antibodies in the combination (see column 5, lines 54-63). The monoclonal antibodies are conjugated to different compatible fluorescent labels including FITC, PE, APC, PerCP, texas red, and coumarin (see column 6, lines 11-29). In the method, a sample is added to a tube containing a diluent, which includes therein, a pre-measured known amount of fluorescent reference microparticles per unit volume (see column 6, lines 54-59). Thereafter, a cocktail of fluorescent-labeled monoclonal antibodies that identify cell surface antigens are added into the sample mixture. The fluorescent microparticles may be labeled by anti-immunoglobulin antibodies having fluorophores conjugated thereto, that are coated into the surface of the particles. Fluorescence therein, is distinguishable from the fluorescence emitted by each one of the fluorescent labels that identify the cell surface antigens; and the fluorescent labels conjugated with each one of the monoclonal antibodies have peak emission spectra each different from the other. The resultant

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sample mixture is incubated and analyzed using multiparametric flow cytometry (see column 4, lines 42-49, column 6, lines 21-30, and column 7, lines 12-24).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the microparticles as taught by Ward, that can be used with any one of blood, spinal fluid or lymph node sample, into the multiparametric flow cytometry method as taught by Nagler, because Ward taught application of the microparticle standard for absolute counting of any combination of cell populations having cell surface antigens specific therefor in order to detect, enumerate, and provide more accurate absolute counts of any selected one or more cell populations present in a cell sample, including phenotypic aberrations of neoplastic cells, as in the method of Naegler.

8. Claims 2, 14 and 26-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nagler et al. (Detection of Minimal residual disease (MRD) after bone marrow transplantation (BMT) by multi-parameter flow cytometry (MPFC), Medical Oncology 16: 177-187 (1999)) in view of Orfao De Matos et al. (US Patent 6,913,901).

Nagler et al. differ from the instant invention in failing to teach culturing the cell sample prior to staining. Nagler et al. also does not teach using reference microparticles as pre-established standards in the method.

Orfao De Matos et al. disclose a flow cytometric method for controlling enumeration of the absolute count of cells in a peripheral blood sample using a mixture of different populations of fluorescent reference microparticles. Orfao De Matos et al.

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provide culturing the cells in vitro (G-CSF) for five days prior to flow cytometrically analyzing and counting the cells using the fluorescent reference microparticles (see Abstract and column 3, lines 55-60). These reference particles are commercially available as contained in a tube having a known number of homogeneously distributed reference microparticles (FLOWCOUNT, TRUCOUNT) in suspension (see column 1, line 62 to column 2, line 10). By using these reference microparticles in flow cytometry, possible existence of specific-positive or negative selection of the cells can be counted (see column 2, lines 41-67). Each population of reference microparticle is uniform; and wherein differing populations of reference particles are composed of multiple microbeads having different size, density, volume, shape, amount of fluorescence, adhesion characteristics, or other physico-chemical properties, depending on the types of cells to be counted (see column 3, lines 1-44 and column 4, lines 1-9). In practice, peripheral blood in parallel sample volumes, are combined with differentially-labeled monoclonal antibodies specific for different cell surface antigens, i.e. CD45 and CD34. Thereafter, different populations of fluorescent reference microparticles conjugated to distinct fluorescent labels, are added to the replicate samples of peripheral blood and then mixed for homogeneous distribution. Light scatter and fluorescence intensity of each of the labeled cells and reference microparticles in the sample mixture, are measured using multiparameter flow cytometry. Analysis of data acquired from the measurements, is performed using software program, i.e. PAINT-Agate, that generates multidimensional data space-based on the flow cytometric measurements, and permits

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identification in the data files of those events corresponding to specific cell types present in heterogeneous cell populations.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the microparticles as taught by Orfao De Matos, into the multiparametric flow cytometry method as taught by Nagler, because Orfao De Matos taught application of the microparticle standard for accurate absolute counting of any combination of cell populations having cell surface antigens specific therefor in order to detect, enumerate, and provide absolute counts of any selected one or more cell populations present in a cell sample, including phenotypic aberrations of neoplastic cells, as in the method of Naegler.

9. No claims are allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (571) 272-0820. The examiner can normally be reached on Monday, Tuesday, and Thursday, 7:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gailene R. Gabel
Patent Examiner
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May 1, 2007

